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Quantification of oesophageal tumour motion and investigation of different image guided correction strategies

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Abstract

Purpose
To accurately quantify oesophageal tumour position variability and to optimize image-guided correction strategies.

Material and methods
Oesophageal cancer patients receiving chemoradiotherapy (41.4-50.4 Gy in 23-28 fractions combined with carboplatin/paclitaxel) were included in a prospective cohort study (NCT02139488). Gold fiducial markers were inserted into the oesophageal tumours during diagnostic endoscopic ultrasound. Four-dimensional (4D) planning computed tomography (CT) and daily 4D-cone beam (CB)CT-scans were acquired. Each CBCT was registered to the planning CT using different regions of interest (bone (3D) and carina, diaphragm, clinical target volume (CTV) and fiducial markers (4D)) for alignment and using the fiducial markers as the true tumour position. Subsequently, a planning target volume (PTV) margin accounting for residual uncertainties including the average respiratory motion was calculated for each of these registrations.

Results
Fifty-six patients with tumours located in the proximal (n=1), mid (n=7) or distal oesophagus (n=25) or at the gastro-oesophageal junction (n=23) were included. A median of 3 fiducials per tumour was inserted. Systematic/random interfraction baseline variation was 0.24/0.35, 0.27/0.47, 0.17/0.26 cm in the left-right (LR), cranial-caudal (CC) and anterior-posterior (AP) direction, respectively. The average peak-to-peak respiratory tumour motion was 0.20, 0.92 and 0.34 cm on the planning CT in LR, CC and AP direction respectively. The required PTV margin with average motion amplitude, depending on the correction strategy used for image-guidance, ranged from 0.8-1.0 cm, 1.1-1.6 cm and 0.7-0.9 cm in LR, CC and AP direction, respectively. A registration based on the CTV resulted in the smallest PTV margins. The registration based on the diaphragm increased PTV margins.

Conclusion
Substantial and anisotropic position variability of oesophageal tumours was observed during radiotherapy, hence non-uniform margins should be considered. Cranial-caudal PTV margins need to be larger than nowadays commonly used. Target positioning during IGRT could be improved with a CTV registration-based correction strategy.

Introduction

Oesophageal cancer is the sixth leading cause of cancer-related death worldwide [1]. Multimodal treatment strategies comprising neoadjuvant chemoradiotherapy (nCRT) plus surgery or definitive chemoradiotherapy (dCRT) have improved survival of patients with locally advanced oesophageal cancer [2-4].
For optimal irradiation of oesophageal cancer, accounting for geometrical uncertainties such as respiratory motion and day-to-day position variability of the tumour is required. To compensate for these uncertainties, planning target volume (PTV) margins are applied. Frequently these margins are generous, isotropic and equal for all patients. Consequently organs at risk adjacent to the CTV are exposed to high levels of irradiation, resulting in increased risk of toxicity of the heart or lungs [5, 6]. Detailed knowledge of the position variability, respiratory motion and identification of the region of interest (ROI) could improve target alignment in oesophageal cancer irradiation.
Image guided radiotherapy (IGRT) has been developed to reduce geometrical uncertainties by acquiring images prior to treatment and making corrections accordingly. Cone Beam computed tomography (CBCT) is currently the state of the art IGRT imaging modality. However, its image quality is lower than diagnostic CT. Bone registration is feasible on CBCT and currently widely used for oesophageal radiotherapy setup. Fiducial markers, placed during endoscopic ultrasound (EUS), can facilitate oesophageal tumour localization on CBCT and have been safely implemented in mediastinal and upper abdominal tumours [7,8]. Although fiducial markers optimize the visibility on CBCT, studies on fiducial-based registration reported conflicting data and currently a fiducial-based registration is not recommended for clinical practice [9].
Therefore, a more robust correction strategy, preferably without fiducial markers, is needed to optimize IGRT. In this study we explored correction strategies on bone, carina, diaphragm and CTV for IGRT alignment of oesophageal tumours. The aims were to quantify interfraction, intrafraction and respiratory motion variability and to investigate the impact of these image-guided correction strategies on the required PTV margins.

Materials and methods

From April 2014 until February 2018 a single center prospective cohort study (NCT02139488) included oesophageal cancer patients who were planned for curative chemoradiotherapy. Chemoradiotherapy regimen consisted of 41.4 Gy (for nCRT) or 50.4 Gy (for dCRT) in 1.8 Gy fractions concurrently given with weekly intravenous paclitaxel (50 mg/m^2) and carboplatin (AUC 2 mg/ml/min).

All included patients underwent diagnostic endoscopy and EUS with fiducial marker placement before the start of treatment. Patients were excluded from the analysis if all fiducials were lost before the planning CT (pCT) or if none of the fiducials were visible on four-dimensional (4D)-CBCT.
Written informed consent was obtained in all patients according to the International Conference of Harmonization/ Good Clinical Practice (ICH/GCP) and national and local regulations. This study was approved by the institute's medical ethical committee.

Staging and marker placement procedure
Staging procedures included a contrast enhanced CT-thorax/abdomen, ^{18}fluorodeoxyglucose positron emission tomography (PET)-CT-scan, an endoscopy and EUS. The endoscopy (Olympus GIF-H180/H190) and EUS (Pentax EG3870UTK/ EG3270UK) were performed under conscious sedation (fentanyl and midazolam). After endoscopic and endosonographic staging, sterile gold fiducial markers (0.35x5.0 mm) (Visicoil, RadioMed, Barlett, USA) were implanted using a 22-gauge cytology EUS needle (Cobra, Sonotip). The goal was to insert three fiducial markers in the tumour (proximal, central and distal) under EUS guidance. If the tumour was stenotic leading to a no-pass during EUS, the distal fiducial was placed as distal as possible or only two fiducials were inserted. No prophylactic antibiotics were prescribed.
Location of the tumour and fiducials were classified according to the American Joint Committee on Cancer manual into four subgroups based on their location: proximal, mid-thoracic, distal and gastro-oesophageal junction (GEJ) [10].

Image acquisition
All patients received a 4DCT (Siemens, Somatom sensation open, Erlangen, Germany) with intravenous contrast (3 mm slice thickness) after fiducial insertion. Oral contrast was not administered to ensure visibility of the fiducial markers. Patients were positioned supine and stabilized with an armrest (ThoraxSupport, MacroMedics, Waddinxveen, Netherlands). A Mid-Position pCT-scan was subsequently reconstructed from the 4DCT-scan for delineation and dose calculation [11, 12]. The GTV was contoured on the pCT by the radiation oncologist with all diagnostic information of diagnostic CT, PET-CT, endoscopy and/or EUS with fine needle aspiration, reflecting clinical practice. Before December 2016 the clinical target volume (CTV) was defined as follows: the CTV comprised the GTV, extended with a 35 mm cranial-caudal (CC) margin and a 5 mm margin in the transverse plane, and was extended to include all pathological lymph nodes. The CTV delineation into the gastric mucosa could be limited to 20 mm. From December 2016 onwards, the clinical delineation protocol was modified according to the adaptations in the national standard; the CTV included the

oesophageal GTV with circumferential borders restricted to the peri-oesophageal fat. The peri-oesophageal fat was delineated for 30 mm in CC direction from the GTV and/or extended to include all pathological lymph nodes. The isotropic CTV to PTV margin in all directions was 10 mm for the first and 12 mm for the second time period.
Daily 4D-CBCT-scans (Synergy 4.6, Elekta Ltd, Crawley, UK; augmented with in-house developed software) were acquired and bony anatomy registration was used for online setup error correction. Once a week, an additional 4D-CBCT-scan was performed immediately after treatment delivery to quantify the intrafraction motion. The imaging dose per scan was approximately 2 cGy.

Tumour position variability analysis
The acquired CBCT images were registered to the pCT by experienced IGRT technologists using chamfer registration algorithm (for bony anatomy (3D) and each fiducial marker individually (4D)) or grey-value registration (for carina, diaphragm or CTV; all 4D). The chamfer registration algorithm segments high densities in the pCT scan and CBCT scan inside the region of interest and minimizes their distance, while the grey value registration uses all grey value information inside the region of interest to optimize the similarity between the images. For the following regions of interest, a rectangular shaped clipbox was used: the bony anatomy, carina, diaphragm and the fiducial markers with a rectangular clipbox per fiducial. The CTV was registered using a shaped region of interest (Fig 1). For readability, the different regions of interest for registration, will now be referred to as bone-registration, carina-registration etc. For the CTV-registration the fiducials were erased from the mask to ensure the fiducials did not influence the CTV-registration.
To the day-to-day positional variability of the oesophageal tumours, the 4D registration results were converted to 3D misalignments by time averaging the displacements per phase in the left-right (LR), CC, and anterior-posterior (AP) direction. Interfraction variability was quantified in terms of grand mean (GM), standard deviation of the patient specific systematic errors (Σ) and root mean square of patient specific random errors (σ) [13]. Peak-to-peak breathing amplitudes were calculated from the minimum and maximum displacements in the 4D-registration over the breathing phases in 3 directions for both pCT as for all 4D-CBCT scans. The interfraction variability was quantified by the fiducial registration corrected for the bone registration that was driving the clinically applied online couch correction. The intrafraction variability was quantified by subtracting the interfraction displacement from the post-treatment marker registration.
To determine which registration resulted in the smallest PTV margins for IGRT setup, the difference between all registrations and the average of the marker registration was calculated, thus assessing the residual error relative to the fiducial markers for each registration.

Statistical analyses were performed using SPSS (IBM statistics, version 22) and Excel (Microsoft, version 14.6.5). Amplitudes of the pCT and CBCT, and comparison of the interfraction variation of the different registrations with the bone-registration were tested by Wilcoxon sign rank test and paired t-test. Results with $p < 0.05$ were considered to be significant.

Margins

Subsequently, the required PTV margin (M) for the different ROI registrations was determined according to the non-linear van Herk formula [13, 14]. The input parameters include the peak-to-peak respiratory amplitude of the tumour (A), the systematic errors ($\sum$: the overall standard deviations of the systematic errors) and random errors (σ: the overall standard deviation of the random errors). Margins were calculated for all patients and per tumour location separately.

$$M = 2.5\times\Sigma + \beta\times\sqrt{\sigma^2 + \sigma_p^2} - \beta\times\sigma_p$$

$$\Sigma = \sqrt{\Sigma^2_{interfraction\ motion} + \Sigma^2_{intrafraction\ Motion}}$$

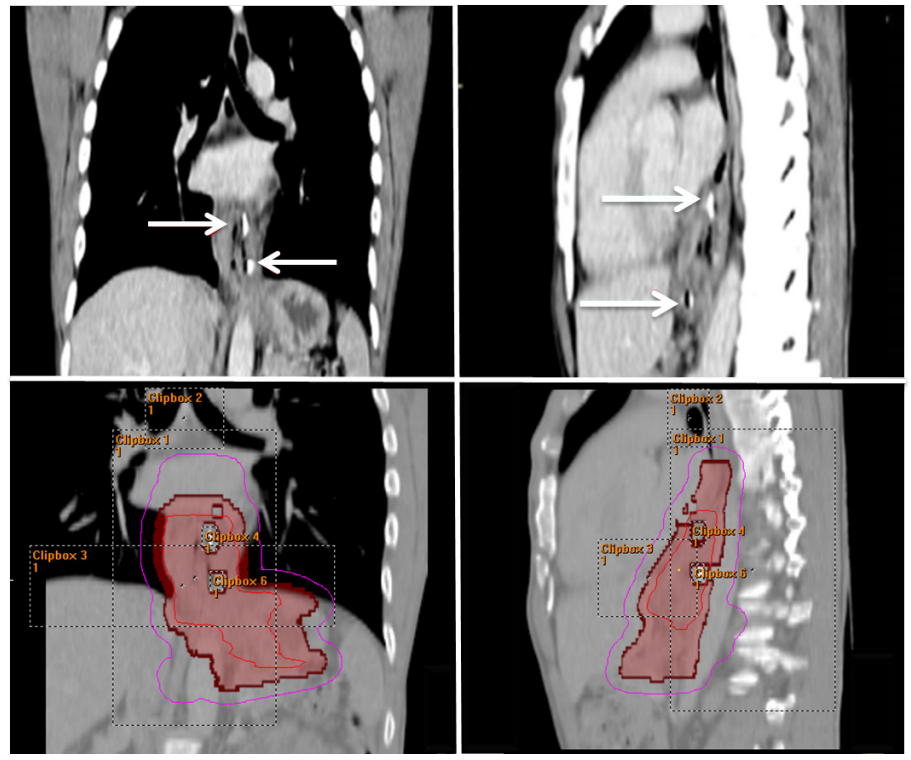
$$\sigma = \sqrt{\sigma^2_{interfraction\ motion} + \sigma^2_{intrafraction\ Motion} + (0.36\times A)^2}$$

Where β is a factor that depends on the prescription dose level (1.64 for 95%) and σ_p a parameter that reflects the penumbra width. Since oesophageal tumours tend to border both to lung and mediastinal tissue, σp was conservatively chosen to reflect the penumbra in water (σ_p = 0.32cm). Margins to cover the CTV with 95% of the prescribed dose for 90% of the patients were calculated to account for the residual geometrical uncertainties for the different regions for registration and corrections, for the complete patient group and per tumour location specific. The average peak-to-peak amplitude of the tumour on the pCT was used for margin calculations of the complete patient group and per tumour location separately. Calculating the intrafraction motion by pre and post-treatment CBCT comparison resembles a worse case scenario. Therefore half of the systematic intrafraction motion was used for the margin calculations.

Marker stability

Using the average marker position as a surrogate of the tumour position, assumes that the position of the markers relative to the tumour is constant. For all fractions, the individual marker position was compared to the center of mass of the fiducials and quantified in terms of systematic and random errors.

FIGURE 1. Planning CT-scan with fiducial markers (white arrows, 2 upper figures) and CBCT-scans (lower figures) with CTV-registration (brown mask) and PTV (pink) contours and the different clipboxes used for different; clipbox 1: bone; 2: carina; 3: diaphragm; 4 and 5: fiducials.



Abbreviations:
CT,computed tomography, CBCT, cone beam computed tomography, CTV, clinical target volume, PTV, planning target volume.

TABLE 1

Baseline characteristics of patients included in this analysis

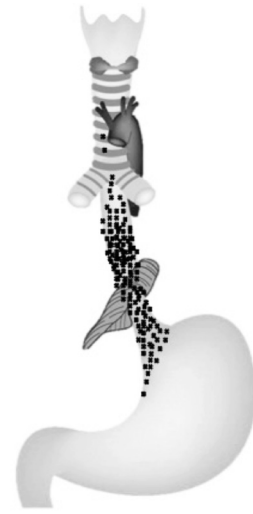
Patients characteristics	**(n=56)**	
Age: median (range) years	64 (37; 84)	
Gender		
Male	40	
Female	16	
Histology		
Adenocarcinoma	46	
Squamous cell carcinoma	9	
Adenosquamous	1	
Location of the primary tumour		
Proximal oesophagus	1	
Middle oesophagus	7	
Distal oesophagus	25	
Gastro-oesophageal junction	23	
Stage[†]		
IB		4
IIA	10	
IIB	10	
IIIA	15	
IIIB	14	
IIIC	3	
Radiation dose		
41.4Gy (23 x 1.8Gy)	51	
50.4Gy (28 x 1.8Gy)	5	
No of fiducials inserted at EUS		
1 fiducial	1	
2 fiducials	16	
3 fiducials	37	
4 fiducials	2	
Total number of fiducials (median/patient)		
No. of inserted fiducials EUS	152	(3)
No. of fiducials at planning CT	126	(2)
No. of fiducials visible on first CBCT	118	(2)
No. of fiducials visible on last CBCT	115	(2)
No. of fiducials visible on last CBCT in all 4D-phases	108	(2)

Abbreviations:
EUS, endoscopic ultrasonography; CT, computed tomography; CBCT, cone beam computed tomography.
[†]According to the 7th Edition of the TNM classification

Results

Sixty-eight eligible patients signed informed consent for this prospective study. Twelve patients were excluded from this analysis for the following reasons. In 7 patients, all inserted fiducial markers were lost. In 3 patients, attenuation of sub-diaphragmatic soft-tissue caused poor visibility of all fiducial markers prohibiting daily 4D-registration in all phases. One patient withdrew from the study and in another patient the 4D-CT reconstruction failed. A total of 56 patients (40 male) with a median age of 64 (range 37-84) years were included in this analysis. Most patients (91%) were treated with neoadjuvant chemoradiotherapy (Table 1).

FIGURE 2. Representation of the locations of the 108 fiducials markers of 56 patients at the planning CT-scan. Each X reflects one fiducial.



Per patient a median of 3 fiducials was inserted in the tumour. In 16/56 patients, tumour stenosis hampered passage of the EUS probe to the distal border, resulting in fiducials in tumour at the proximal border, middle part and as distal as possible. This most distal fiducial was located at a median of 2 cm cranial of the distal tumour border as determined during endoscopy. No adverse events related to the EUS fiducial insertion procedure (i.e., no infection, perforation, bleeding) occurred. Out of 152 implanted fiducials, 126 were visible on the pCT (all 126 located in the oesophageal tumour mass) and 118 on the first CBCT (Table 1). In total 115/118 fiducials that were identified on the first CBCT remained visible during the complete treatment period. However, 7 of these 115 fiducials were not visible in all 4D-CBCT phases which prohibited 4D-CBCT registration.

Figure 2 shows the location of the 108 inserted fiducials in 56 patients. A total of 1453 4D-CBCT scans were evaluable, on average 26 per patient.

Marker stability

The individual marker position compared to the center of mass over the treatment period showed a systematic and random error of 0.09 and 0.08 cm, respectively.

Interfraction variability

The systematic interfraction variation of tumour position relative to the bone-registration was 0.24, 0.27 and 0.17 cm in the LR, CC and AP direction respectively, while the random baseline variation was 0.35, 0.47 and 0.26 cm, respectively. The residual interfraction variability for correction strategies based on the different registrations (bone-registration, carina-registration, diaphragm-registration and CTV-registration) are shown in Table 2. The largest systematic error was seen in CC direction. The CTV-registration reduced the systematic error of the tumour in LR (p<0.001) and CC (p=0.049) direction. The carina-registration reduced the systematic error in CC direction (p<0.001), but significantly increased in AP direction (p=0.02). While the diaphragm-registration significantly increased the systematic error in both CC (p=0.01) and AP (p<0.001) direction.

Intrafraction variability

The average (range) peak-to-peak amplitude of the oesophageal tumour on the pCT was 0.20 (0.1-0.6), 0.92 (0.2-2.3) and 0.34 (0.0-1.2) cm in LR, CC and AP respectively (Table 3). The average peak-to-peak amplitude of the tumour during treatment was 0.17, 0.88 and 0.31 cm respectively, not significantly different from the pCT (p=0.07, p=0.49, p=0.27 respectively). The group mean amplitude difference between pCT and CBCT during treatment was 0.03, 0.02 and 0.03 cm in LR, CC and AP respectively, while the systematic/random amplitude difference was 0.13/0.13, 0.35/0.19 and 0.19/0.18 cm respectively.

Margins

Margins per registration and per tumour location, calculated with the average breathing amplitude, are presented in Table 4. The bone-registration requires a PTV margin of 1.0 cm in LR, 1.3 cm in CC and 0.7 cm in AP direction. The CTV-registration resulted in the smallest PTV margins, with a LR, CC and AP margin of 0.8, 1.1 and 0.7 cm respectively. An increase of the required margins was seen with the diaphragm-registration. The influence of amplitude motion on PTV margins of a CTV-registration is presented in Supplementary Figure 1.

TABLE 2

Interfraction tumour position variability relative to the different registrations. The grand mean (GM), SD of systematic errors (Σ), root mean square of random errors (σ) of the bone, carina, diaphragm and CTV-registration based setup strategy

Variability	LR (cm)	CC (cm)	AP (cm)
Bone-registration			
GM	0.07	-0.13	0.05
Σ	0.24	0.27	0.17
σ	0.35	0.47	0.26
Carina-registration†			
GM	0.03	-0.17	-0.18
Σ	0.25	0.23*	0.23‡
σ	0.35	0.38*	0.33‡
Diaphragm-registration†			
GM	-0.01	0.08	-0.14
Σ	0.24	0.34‡	0.23‡
σ	0.34	0.54	0.38‡
CTV-registration†			
GM	-0.03	-0.03	-0.01
Σ	0.21*	0.24*	0.18
σ	0.29*	0.35*	0.27

Abbreviations:
LR, left-right; CC, cranial-caudal; AP, anterior-posterior; cm, centimeters; GM, grand mean; ROI, region of interest; SD, standard deviation; Σ, systematic error; σ, random error, CTV, clinical target volume.

† Systematic and random errors of carina-registration, diaphragm-registration and CTV-registration were compared with bone-registration. Numbers marked with a ‡ represent statistical significant increase and marked with * represent statistical significant decrease of the registration compared to the bone-registration.

TABLE 3

Amplitudes of the fiducial marker motion measured on the 4D-planning-CT and 4D-CBCT for all patients and intrafraction fiducial marker variability between pre-treatment and post-treatment CBCT.

Variability	LR (cm)	CC (cm)	AP (cm)
Amplitudes pCT			
Average	0.20	0.92	0.34
Standard deviation	0.12	0.37	0.22
Range	0.1-0.6	0.2-2.3	0.0-1.2
Average (range) of amplitudes on pCT by tumour location			
Mid+proximal	0.15 (0.1-0.2)	0.73 (0.2-1.4)	0.15 (0-0.4)
Distal	0.22 (0.1-0.6)	0.97 (0.5-1.7)	0.38 (0.1-0.8)
GEJ	0.20 (0.1-0.5)	0.93 (0.5-2.3)	0.38 (0.1-1.2)
Amplitudes CBCT			
Average	0.17	0.88	0.31
Standard deviation	0.07	0.35	0.16
Range	0.06-0.43	0.13-1.84	0.04-0.64
Amplitude difference pCT and CBCT			
GM	0.03	0.02	0.03
Σ	0.13	0.35	0.19
σ	0.13	0.19	0.18
Intrafraction position variability			
GM	0.06	0.02	-0.11
Σ	0.14	0.19	0.09
σ	0.23	0.19	0.17

Abbreviations:
4D, four-dimensional; LR, left-right; CC, cranial-caudal; AP, anterior-posterior; cm, centimeters; pCT, planning computed tomography; CBCT, conebeam computed tomography; GM, grand mean; Σ, systematic error; σ, random error; GEJ, gastro-oesophageal junction.

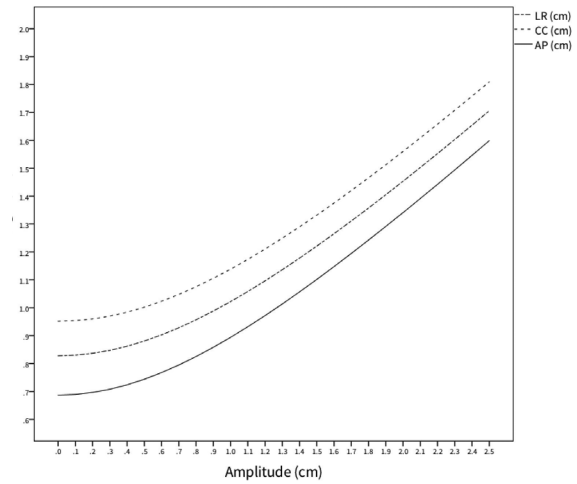
TABLE 4

PTV margins for different registration strategies for all patients and separately per tumour location. The average marker position was taken as a surrogate of the tumour position and margins were calculated with the average breathing amplitude of the CTV region of interest on the planning CT.

	All patients n=56			GEJ n=23			Distal n=25			Mid+Prox n=8		
	Margin (cm)			Margin (cm)			Margin (cm)			Margin (cm)		
	LR	**CC**	**AP**	**LR**	**CC**	**AP**	**LR**	**CC**	**AP**	**LR**	**CC**	**AP**
Correction strategy												
Bone	1.0	1.3	0.7	1.1	1.4	0.8	0.9	1.4	0.6	0.7	0.9	0.4
Carina	1.0	1.1	0.9	1.2	1.2	1.0	1.0	1.2	0.8	0.6	0.7	0.7
Diaphragm	1.0	1.6	0.9	1.2	1.5	1.1	0.8	1.6	0.8	0.9	1.5	1.0
CTV	0.8	1.1	0.7	1.1	1.2	0.9	0.7	1.2	0.6	0.4	0.7	0.5

Abbreviations:
LR, left-right; CC, cranial-caudal; AP, anterior-posterior; cm, centimeters; GEJ, gastro-oesophageal junction; CTV, clinical target volume, CT, computed tomography

SUPPLEMENTARY FIGURE 1: PTV margin as function of the peak-to-peak amplitude (cm) for registration on the CTV mask for LR (solid line), CC (dashed line) and AP (dashed-dotted line).



Abbreviations:
PTV, planning target volume; CTV, clinical target volume; LR, left-right; CC, cranial-caudal; AP, anterior-posterior; cm, centimetres

Discussion

Interfraction and intrafraction motion of oesophageal tumours were analysed in 56 patients on daily pre-treatment and weekly post-treatment 4D-CBCT-scans by using fiducial markers. Substantial and anisotropic tumour motion variability was observed, indicating that anisotropic PTV margins should be considered. This study showed that PTV margins could be reduced with a CTV-registration and carina-registration compared to bone-registration.

The different registration strategies in relation to the fiducials in the primary tumour (GTV) were investigated. Accurate alignment of both CTV and GTV is required for optimal irradiation, especially when simultaneous integrated boost (SIB) techniques are applied. Although a GTV-registration could potentially reduce systematic and random errors even further, appropriate CTV coverage is required for the success of the treatment. Therefore, a CTV-registration was investigated. Further, motion of the lymph nodes at distance of the GTV was not assessed in this study, as markers were inserted in the primary tumour only. In lung cancer patients, differential motion between tumour and lymph nodes was observed and a carina-based setup was shown to be beneficial [15]. For oesophageal cancer, a carina-registration was previously explored in 24 patients and registration was feasible in 95% of the CBCT scans [16]. An increase of the systematic and random error with a carina-registration was observed, resulting in larger PTV margins. In the current series, the carina-registration significantly increased the systematic and random error in AP direction relative to a bone-registration, leading to an increase of the AP margin. Unfortunately, sample sizes for analysis of subgroups per tumour location were too small for strong conclusions. Future studies should investigate if location specific correction strategies could be beneficial.

Diaphragm-registration was explored since the diaphragm is adjacent to the distal oesophagus and GEJ. Unfortunately, registration on the diaphragm resulted in increased positioning uncertainty. The diaphragm deforms during inspiration and the semicircle flattens to a straighter shape. A rigid registration on this deforming diaphragm might lead to rotations and possibly explains its decreased accuracy for setup.

Over all, respiratory motion amplitude was largest in the cranial-caudal direction and the magnitude of motion depended on the tumour location. Previous studies found similar results; motion of tumours located below the diaphragm showed a larger motion than thoracic tumours [17-19]. For most oesophageal cancer patients, radiotherapy is currently delivered after bone setup correction. To improve oesophageal cancer radiotherapy a marker-based setup seems an obvious approach, and is currently standard of care in other tumour sites (e.g. prostate cancer or bladder cancer) [20,21].

However, we used fiducial markers for localization of the tumour but advocate a registration without fiducial markers for oesophageal IGRT for the following reasons. First, although we did not experience adverse events of the fiducial insertion in our cohort, others reported adverse events in 4/30 oesophageal cancer patients [22]. Second, the current study shows that in 10% of the patients all fiducials were detached and only 76% (115/152) of the fiducials remained visible until the last CBCT. Jin et al. reported similar results; only 60% (60/101) of the fiducials remained visible on CBCT during the complete treatment period [9]. And last, oesophageal marker displacement was observed in a selection of patients, caused by tumour shrinkage, marker migration or shape variation of the oesophagus and proximal stomach. Likewise, Liu et al. [18] reported a moderate correlation between fiducials and primary tumour motion, but results were patient-specific and differential fiducial motion was observed. Therefore marker-based registration was only suitable in a selection of patients. Jin et al. also found considerable fluctuations of the pairwise distance of the fiducial markers due to tissue deformation and concluded that a marker-based registration was not feasible for clinical use [9]. Hence, the invasiveness of EUS insertion, frequent detachment of fiducial markers and possible fiducial displacements stresses the need for fiducials-less IGRT setup correction strategy for oesophageal cancer.

Our results show that the required PTV margins are still substantial, even with state-of-the art oesophageal IGRT. Furthermore, in the current series, the 4D-CT was reconstructed as a Mid-position CT. Treatment volumes will increase even further without a 4D-technique or with an internal target volume strategy instead of a Mid-position strategy [23]. Notably, the random error was larger than the systematic error, indicating anatomical variation, deformation or tumour response might have influenced these errors. Furthermore, other uncertainties as marker surrogate error, rotations and delineation errors were not included in the margin calculation. PTV margins should be increased even further, to account for these uncertainties. Cranial-caudal PTV margins need to be larger than nowadays commonly used. Future studies should analyse if improved soft tissue contrast and daily replanning, e.g. with a Magnetic Resonance Imaging-Linac (MRL), is feasible for oesophageal cancer. With the aim to further reduce margins and thus normal tissue toxicity, treatment delivery on the MRL may further improve accurate dose delivery.

For patients treated with dCRT, local in-field recurrence still occurs in about half of the patients [24] and currently phase II/III prospective dose escalation trials are including patients for SIB GTV boost strategies [25,26]. In these studies, isotropic PTV margins to the (internal) CTV and (internal) GTV of 0.5 and 0.3 cm respectively [26] and 1.0 cm and 1.0 cm respectively [27] are applied. For a substantial group of patients, these margins are too small to ensure complete target coverage, especially in CC direction. Accurate delivery without geometrical miss of this additional boost is essential for the success of these trials.

Also, with pathological complete response rates of 23-49% [28] there is a trend towards the development of organ-preservation strategies for the clinical complete responders after nCRT [29,30]. For these patients, who may be cured by chemoradiotherapy alone, a geometrical miss could potentially lead to non-complete response and inevitable lead to oesophagectomy. Therefore, an accurate setup correction strategy is needed for both operable and inoperable oesophageal cancer patients treated with chemoradiotherapy.

Conclusions

In this prospective study we observed substantial and anisotropic position variability of the oesophageal tumour during radiotherapy. Variability was largest in the cranial-caudal direction. Cranial-caudal PTV margins need to be larger than nowadays commonly used to ensure target coverage. Margins were calculated to compensate for the interfraction and intrafraction variability and need to be increased even further to compensate for other uncertainties such as target definition or marker surrogate errors. In order to further improve oesophageal IGRT, anisotropic patient specific margins should be considered. IGRT setup correction with a CTV-registration is promising for further improving treatment accuracy in oesophageal cancer.

References

1 Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in europe: Estimates for 40 countries in 2012. European journal of cancer 2013;49:1374-1403.
2 Gwynne S, Hurt C, Evans M, et al. Definitive chemoradiation for oesophageal cancer--a standard of care in patients with non-metastatic oesophageal cancer. Clin Oncol (R Coll Radiol) 2011;23:182-188.
3 Shapiro J, van Lanschot JJB, Hulshof M, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (cross): Long-term results of a randomised controlled trial. The Lancet. Oncology 2015;16:1090-1098.
4 Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: An updated meta-analysis. The Lancet. Oncology 2011;12:681-692.
5 Beukema JC, van Luijk P, Widder J, et al. Is cardiac toxicity a relevant issue in the radiation treatment of esophageal cancer? Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2015;114:85-90.
6 Lin SH, Zhang N, Godby J, et al. Radiation modality use and cardiopulmonary mortality risk in elderly patients with esophageal cancer. Cancer 2016;122:917-928.
7 DiMaio CJ, Nagula S, Goodman KA, et al. Eus-guided fiducial placement for image-guided radiation therapy in gi malignancies by using a 22-gauge needle (with videos). Gastrointestinal endoscopy 2010;71:1204-1210.
8 Schaake EE, Belderbos JS, Buikhuisen WA, et al. Mediastinal lymph node position variability in non-small cell lung cancer patients treated with radical irradiation. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2012;105:150-154.
9 Jin P, van der Horst A, de Jong R, et al. Marker-based quantification of interfractional tumor position variation and the use of markers for setup verification in radiation therapy for esophageal cancer. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2015;117:412-418.
10 Rice TW, Blackstone EH Rusch VW. 7th edition of the ajcc cancer staging manual: Esophagus and esophagogastric junction. Annals of surgical oncology 2010;17:1721-1724.
11 Wolthaus JW, Sonke JJ, van Herk M, et al. Reconstruction of a time-averaged midposition ct scan for radiotherapy planning of lung cancer patients using deformable registration. Medical physics 2008;35:3998-4011.
12 Kruis MF, van de Kamer JB, Belderbos JS, et al. 4d ct amplitude binning for the generation of a time-averaged 3d mid-position ct scan. Physics in medicine and biology 2014;59:5517-5529.
13 van Herk M. Errors and margins in radiotherapy. Seminars in radiation oncology 2004;14:52-64.
14 van Herk M, Remeijer P, Rasch C, et al. The probability of correct target dosage: Dose-population histograms for deriving treatment margins in radiotherapy. International journal of radiation oncology, biology, physics 2000;47:1121-1135.
15 Schaake EE, Rossi MM, Buikhuisen WA, et al. Differential motion between mediastinal lymph nodes and primary tumor in radically irradiated lung cancer patients. International journal of radiation oncology, biology, physics 2014;90:959-966.
16 Machiels M, Jin P, van Gurp CH, et al. Comparison of carina-based versus bony anatomy-based registration for setup verification in esophageal cancer radiotherapy. Radiat Oncol 2018;13:48.
17 Jin P, Hulshof MC, de Jong R, et al. Quantification of respiration-induced esophageal tumor motion using fiducial markers and four-dimensional computed tomography. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2016;118:492-497.
18 Liu F, Ng S, Huguet F, et al. Are fiducial markers useful surrogates when using respiratory gating to reduce motion of gastroesophageal junction tumors? Acta Oncol 2016;55:1040-1046.

19 Yaremko BP, Guerrero TM, McAleer MF, et al. Determination of respiratory motion for distal esophagus cancer using four-dimensional computed tomography. International journal of radiation oncology, biology, physics 2008;70:145-153.
20 Pos F, Bex A, Dees-Ribbers HM, et al. Lipiodol injection for target volume delineation and image guidance during radiotherapy for bladder cancer. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2009;93:364-367.
21 van der Heide UA, Kotte AN, Dehnad H, et al. Analysis of fiducial marker-based position verification in the external beam radiotherapy of patients with prostate cancer. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2007;82:38-45.
22 Machiels M, van Hooft J, Jin P, et al. Endoscopy/eus-guided fiducial marker placement in patients with esophageal cancer: A comparative analysis of 3 types of markers. Gastrointestinal endoscopy 2015;82:641-649.
23 Jin P, Machiels M, Crama KF, et al. Dosimetric benefits of midposition compared with internal target volume strategy for esophageal cancer radiation therapy. International journal of radiation oncology, biology, physics 2019;103:491-502.
24 Welsh J, Settle SH, Amini A, et al. Failure patterns in patients with esophageal cancer treated with definitive chemoradiation. Cancer 2012;118:2632-2640.
25 Hulshof MC. Dose escalation study for inoperable esophageal cancer patients. Ntr3532. In: http://www.trialregister.nl, ed., 2012.
26 Welsh JW, Seyedin SN, Allen PK, et al. Local control and toxicity of a simultaneous integrated boost for dose escalation in locally advanced esophageal cancer: Interim results from a prospective phase i/ii trial. J Thorac Oncol 2017;12:375-382.
27 Hulshof MC. Dose escalation study for inoperable esophageal cancer patients. Nederlands trial register (http://www.trialregister.nl). NTR3532, 2012.
28 van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. The New England journal of medicine 2012;366:2074-2084.
29 Noordman BJ, Spaander MCW, Valkema R, et al. Detection of residual disease after neoadjuvant chemoradiotherapy for oesophageal cancer (presano): A prospective multicentre, diagnostic cohort study. The Lancet. Oncology 2018.
30 Noordman BJ, Wijnhoven BPL, Lagarde SM, et al. Neoadjuvant chemoradiotherapy plus surgery versus active surveillance for oesophageal cancer: A stepped-wedge cluster randomised trial. BMC Cancer 2018;18:142.

Oesophageal tumour motion and IGRT
Chapter 7